REMARKS

In light of the foregoing amendments and following remarks, reconsideration and withdrawal of each rejection is respectfully solicited.

Introduction and Support for Claim Amendments:

Before entry of the foregoing amendment, claims 64-83 were pending. Upon entry of the foregoing amendment, claims 64-66, 69, 71, 72, 74, 76-82 will be cancelled; claims 70, 73, 75, and 83 will be amended; and claims 84-90 will be added. Claims 84 and 85 are the only independent claims.

Each claim amendment and newly presented claim is supported by the specification as originally filed. For instance, support for the phrase "wherein said framework regions correspond to the framework regions contained in a sequence selected from the group consisting of..." in claims 73 and 75 can be found, e.g., at page 39, lines 13-16; page 16, lines 26-29; page 10, lines 19-21; page 8, lines 30-33; and page 6, lines 28-32 of the specification. Support for sub-section (a) of independent claim 84 exists, for example, at page 5, lines 23-25 of the specification, while support for sub-section (b) thereof exists, inter alia, at page 219, originally filed claim 38; and page 8, lines 30-33 of the specification. Support for independent claim 85 exists, for example, at page 5, lines 23-25; page 10, lines 29-31 of the specification; and page 8, lines 12-15. Support for dependent claim 86 exists, e.g., at page 10, lines 33-37 of the specification.

Amendment to Specification:

Applicants have corrected a typographical error in the "related applications" section at the beginning of page 1 of the Specification, which was introduced by way of a preliminary amendment filed on January 24, 2000.

Rejections under 35 U.S.C. § 102:

The only rejections outstanding in the instant case are anticipation rejections based on three different prior art references. To this end, the Examiner rejected claims 64-67 and 83 under 35 U.S.C. § 102(b) as being anticipated by Sigma Catalogue Number D1915, D2040, D2165, D2290 (1993) ("Sigma"). Claims 64-68 also stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Maneewannakul et al. (Plasmid (1994) Vol. 31, page s 300-307) ("Maneewannakul"). In addition, the Examiner alleges that claims 64-68, 71, 72, 74, 77, 78, 80, 83 (and those dependent therefrom) are anticipated under 35 U.S.C. 102(e) by US Patent No. 5,693,493 issued to Robinson et al. ("Robinson"). Applicants respectfully traverse each of the rejections.

In particular, Applicants respectfully urge the withdrawal of the rejections, since neither Sigma nor Maneewannakul nor Robinson teaches each feature of the claimed invention. For example, neither Sigma nor Maneewannakul nor Robinson discloses or suggests a modular replicable vector containing a plurality of vector modules, where each vector module is (i) flanked by unique DNA cleavage sites and (ii) essentially devoid of the DNA cleavage sites contained in a nucleotide sequence selected from the group of V-

kappa-1(SEQ ID NO: 42), V-kappa-2 (SEQ ID NO: 44), V-kappa-3 (SEQ ID NO: 46), V-kappa-4 (SEQ ID NO: 48), V-lambda-1 (SEQ ID NO: 50), V-lambda-2 (SEQ ID NO: 52), V-lambda-3 (SEQ ID NO: 54), VH1A (SEQ ID NO: 56), VH1B (SEQ ID NO: 58), VH2 (SEQ ID NO: 60), VH3 (SEQ ID NO: 62), VH4 (SEQ ID NO: 64), VH5 (SEQ ID NO: 66), and VH6 (SEQ ID NO: 68) at the boundaries between each consensus framework region and each complementarity determining region--which is required by independent claim 84.

Furthermore, neither Sigma nor Maneewannakul nor Robinson teaches or suggests a modular replicable vector that contains: (i) a nucleotide sequence encoding an immunoglobulin variable heavy or light region containing a modular sequence of four consensus framework regions interspaced by three CDR's, where the nucleotide sequence contains DNA cleavage sites at the boundary of each consensus framework region and each complementarity determining region, and (ii) a plurality of vector modules, each of which is flanked by DNA cleavage sites, where each of the DNA cleavage sites contained in (i) and (ii) is unique within the vector--which is required by independent claim 85.

Objected-to Claims:

Claims 69, 70, 73, 75, 76, 79, 81, and 82 are objected to as being dependent upon an allegedly rejected base claim. In light of Applicants remarks concerning the allowability of the base claims, Applicants respectfully request the objections be withdrawn.

Brief Description of Concurrently Submitted Prior Art:

Applicants also submit concurrently herewith a supplemental Information Disclosure Statement for consideration by the Examiner and respectfully submit that all pending, amended and new claims are patentable over the cited prior art. Applicants' summary of these references follows.

U.S. Patent No. 5,476,786 to Huston relates to synthetic chimeric scFv polypeptides that contain "amino acid sequences homologous to portions of the CDRs of the variable domain of one immunoglobulin light or heavy chain, and other sequences homologous to the framework regions, or FRs, of the variable domain of a second, different immunoglobulin light or heavy chain" (col. 3, lines 20-25). One method for making a synthetic chimeric polypeptide involves the construction of three CDR-encoding polynucleotide sequences (described as X_1, X_2 and X_3), where "[e]ach of the sequences contain restriction sites proximal its 3' and 5' ends, and each is flanked by polynucleotide sequences (FR_1, FR_2, FR_3 and FR_4) encoding selected framework region (FR) amino acid sequences homologous to a portion of the variable domain of an immunoglobulin. This DNA has the structure:

$$R_1\text{-}FR_1\text{-}X_1\text{-}FR_2\text{-}X_2\text{-}FR_3\text{-}X_3\text{-}FR_4\text{-}R_2$$

where R_1 is a 5' phosphate group or polynucleotide sequence and R_2 is a 3' hydroxyl group or polynucleotide sequence. The X polynucleotide sequences may be selectively excised using restriction enzymes and replaced by other DNA sequences

encoding the CDR amino acid sequences of a variable domain of a selected immunoglobulin. This type of DNA sequence may encode at least part of the variable region of either or both a heavy or light chain of an immunoglobulin..." (col. 4, lines 38-57; col. 6, lines 1-9). "In one preferred embodiment, the biosynthetic antibody binding site comprises FRs homologous with a portion of the FRs of a human immunoglobulin and CDRs homologous with CDRs from a mouse immunoglobulin" (col. 3, lines 30-34).

de Kruif et al., JMB 248:97-105 (1995) ("de Kruif") reports on the construction of a phage display library of "semi-synthetic" human scFv fragments having a randomized HCDR3 region. According to de Kruif, "Semi-synthetic VH regions" were constructed "by fusing 49 different human VH gene segments... to CDR3 regions of 6 to 15 amino acid residues in length" (p. 98, right col., first full para.). "The semi-synthetic VH regions were cloned into seven vectors containing light chains encoded by members of the Vκ1 to Vκ4 and Vλ1 to Vλ3 gene families. Individual libraries were combined to form a single library of approximately 3.6 X 10^8 clones" (Id.). de Kruif cautions that "fully randomized HCDR3 regions may not be desirable..." (Id. at 101, right col., first full para.).

Barbas et al., PNAS (USA) 89:4457-4461 (1992) ("Barbas") describes a method of constructing a library of heavy chain (Fd) fragments having a randomized HCDR3 region. Variability of the HCR3 sequence was achieved by PCR. Thus, Barbas states, "[a]n oligonucleotide was synthesized that is complementary to 18 bases on both the FR3 and FR4 sides of CDR3 with a randomised sequence in the central 48 bases corresponding to

the actual CDR. PCRs with this oligonucleotide and one complementary to the 3' end of the gene provided a gene fragment that encodes from the end of FR3 to the end of the Fd fragment. The other half of the gene was also produced by PCR. These two products were then combined and fused in a final PCR (Fig. 1)" (page 4458, right col., first full para.).

Schier et al., Gene 169:147-55 (1996) ("Schier") discloses a technique for mutagenizing three hyperviable regions (L1, L3 and H2) of an scFv, conventionally known today as LCDR1, LCDR3 and HCDR2, respectively (page148, right col., last para.). According to Schier, HCDR3 was not selected for mutagenesis "due to its [relatively long] length" (Id.). The particular mutagenesis technique used by Schier, termed "parsimonious mutagenesis" ("PM"), involves the use of mutagenic oligonucleotides designed to minimize coding sequence redundancy and limit the number of amino acid residues that do not retain parental structural features (see abstract). The PM-randomised scFv gene repertoire was assembled by splicing together three overlapping PCR fragments, each of which contained a portion of the wild type scFv and mutagenized LCDR1, LCDR3 or HCDR2 (see page 149, right col., last para.; page 151, left col.).

Garrard and Henner, Gene 128:103-109 (1993) ("Garrard") discloses the construction of Fab libraries having 4 randomized CDR regions (LCDR1, LCDR3, HCDR2 and HCDR3), obtained by PCR techniques (see page 104, left col., last para.). According to Garrard, plasmid pDH198 (which encodes a Fab) was used as the

"backbone" sequence and various "PCR primers with degeneracy in selected sights" were used to generate diversity (See page 104, right col., Figure 1 caption). Using this PCR-based approach, one light-chain library and two heavy-chain libraries (DH and LG) were generated (See id.). "After PCR, the DNA encoding the light-chain library was restricted with BstEII and Asp718 and ligated [into a vector]" (Id.). "Each of the two randomised heavy-chain PCR products...were restricted with BssHII and NcoI before ligating [into the vectors containing the randomised light chain product]" (Id.).

U.S. Patent No. 5,840,479 issued to Little et al. relates to the preparation and use of gene banks of synthetic human antibodies having hypervariable regions formed by "almost randomly" combined oligonucleotides (see abstract). According to Little, randomisation of the hypervariable regions was restricted by six limitations in order to: allow for positions in the sequence for certain conserved amino acids, reduce the number of stop codons, and incorporate a new restriction site (see col. 2, lines 3-31). Each heavy and light chain was synthesized in multiple segments (i.e., H1-H8 and L1-L6), ligated by the oligonucleotide base overlaps (shown in Table 1 of the patent), and amplified using PCR (see Table 1, col. 5, line 13 through col. 6, line 5).

Conclusion:

In view of the foregoing, Applicants respectfully request the Examiner to withdraw each rejection and pass the claims to allowance. The Examiner is invited to contact the undersigned attorney to resolve any issues, in order to expedite the prosecution of the

application.

Respectfully submitted,

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Marked-up Version of Amended Claims

70. The vector according to claim 84, wherein said vector is selected from the group consisting of pCAL 4 (SEQ ID NO: 274), pCALO-1 (SEQ ID NO: 294), pCALO-2 (SEQ ID NO: 296), ~~and~~ pCALO-3 (SEQ ID NO: 299) and pMCS (SEQ ID NO: 264).

73. The vector according to claim ~~72~~ 85, wherein said framework regions correspond to the framework regions contained in a ~~nucleotide~~ sequence ~~encoding an immunoglobulin light chain variable region is~~ selected from the group consisting of V.kappa.1 (SEQ ID NO: 42), V.kappa.2 (SEQ ID NO: 44), V.kappa.3 (SEQ ID NO: 46), and V.kappa.4 (SEQ ID NO: 48), V.lambda.1 (SEQ ID NO: 50), V.lambda.2 (SEQ ID NO: 52), and V.lambda.3 (SEQ ID NO: 54.

75. The vector according to claim ~~72~~ 85, wherein said framework regions correspond to the framework regions contained in a ~~nucleotide~~ sequence ~~encoding an immunoglobulin heavy chain variable region is~~ selected from the group consisting of VH1A (SEQ ID NO: 56), VH1B (SEQ ID NO: 58), VH2 (SEQ ID NO: 60), VH3 (SEQ ID NO: 62), VH4 (SEQ ID NO: 64), VH5 (SEQ ID NO: 66), and VH6 (SEQ ID NO: 68).

83. The vector according to claim ~~66~~ 84, wherein said vector is a phagemid vector.